May 12, 2005

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GlaxoSmithKline

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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket 1998D-0514
Draft Guidance for Industry on Abbreviated New Drug Applications: Impurities in Drug Substances; Chemistry, Manufacturing, and Controls Information

To Whom It May Concern::

Enclosed please find specific comments from GlaxoSmithKline for the Draft Guidance for Industry on Abbreviated New Drug Applications: Impurities in Drug Substances; Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The specific comments are presented in order by line number and section in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye Smith Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

98D-0514

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Specific Comments:

The following comments are provided with the Section and line number referenced.

Line number	Section	Comment
103 - 105	III. A.	Acceptance criteria should be based on safety considerations, not on the quantitation or detection limit of the analytical method. This statement should be modified.
104 - 105	III. A.	"...level at which the impurities are expected to be controlled." is not clear. The statement should be clarified so that it means the justified maximum level is based on safety considerations.
135 – 137	III. B.	ICH Q3(A) requires acceptance criteria in NDAs to be set based not only on qualification, but also on typical levels found in manufacture, which may be lower. The same criteria should also apply to companies submitting ANDAs. If existing companies can meet the USP limit there is no justification for allowing other companies requesting that the limit is raised, since this increases the risk to the patient. This statement should be modified in this guidance.
141 - 142	III. B.	The ANDA sponsor should ensure that acceptance criteria for impurities in its drug product reflect levels found in the approved human drug product. This may require lower acceptance criteria in the drug substance. This information should be included in this guidance.
163 - 164	IV.	The ANDA sponsor should ensure that acceptance criteria for impurities in its drug product reflect levels found in the approved human drug product. This may require lower acceptance criteria in the drug substance. This information should be included in this guidance.
165	IV.	Clarify that "metabolite" means "human metabolite".
168 -170	IV.	Clarify the meaning of "in vitro genotoxicity studies". As such, can a study of this nature sufficiently qualify an impurity as is implied?
197 – 199	IV. B.	If an impurity is evaluated using impurities with the drug substance, this could lead to unrealistically high qualified levels. The reason for this is that genotoxicity depends on the total amount given. So, below a certain threshold, a genotoxic agent will not be detectable. The concentration of the impurity in the drug substance at that level will depend on how much drug can be given before toxicity is seen from the drug itself. Therefore, this sentence should be clarified.
203 - 205	IV. B. 1.	The ANDA sponsor should ensure that acceptance criteria for impurities in its drug product reflect levels found in the approved human drug product. This may require lower acceptance criteria in the drug substance. This information should be included in this guidance.
223 – 231	IV. B. 3.	For NCE's, general toxicity studies are normally required in addition to genotoxicity studies in order to qualify an impurity. The same should apply in ANDAs.